# Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/DK05/000127

International filing date: 24 February 2005 (24.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: DK
Number: PA200400326
Filing date: 27 February 2004 (27.02.2004)

Date of receipt at the International Bureau: 24 March 2005 (24.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

# Kongeriget Danmark

Patent application No.: PA 2004 00326

Date of filing: 27 February 2004

Applicant:
(Name and address)

H. Lundbeck A/S
Ottiliavej 9
DK-2500 Valby
Denmark

Title: Crystalline forms of a pharmaceutical compound

IPC: -

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

Patent- og Varemærkestyrelsen
Kongeriget Danmark

**Patent- og Varemærkestyrelsen**
Økonomi- og Erhvervsministeriet

18 March 2005

Susanne Morsing

PATENT- OG VAREMÆRKESTYRELSEN

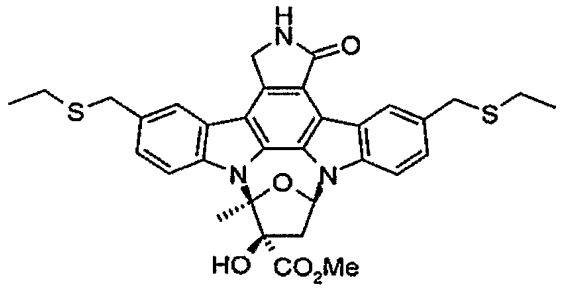
# CRYSTALLINE FORMS OF A PHARMACEUTICAL COMPOUND

## FIELD OF THE INVENTION

The present invention relates to crystalline forms of a compound and the use of such forms in the preparation of a medicament, in particular for the treatment of Parkinson's disease.

## BACKGROUND OF THE INVENTION

The compound with the structure outlined below is presently in clinical trials for Parkinson's disease (Idrugs, 2003, 6(4), 377-383):




This compound is in the following referred to as Compound I. The chemical name of Compound I is [9S- (9α, 10β, 12α)]- 5, 16- *Bis* [(ethylthio) methyl]-2, 3, 9, 10, 11, 12-hexahydro- 10- hydroxy- 9- methyl- 1- oxo- 9, 12- epoxy- 1H- diindolo [1, 2, 3-fg: 3', 2', 1'-kl] pyrrolo [3, 4-i] [1, 6] benzodiazocine- 10-carboxylic acid methyl ester.

The following references relates to Compound I, in particular to methods for its preparation [J.Med. Chem. 1997, 40(12), 1863-1869; Curr. Med. Chem. - Central Nervous System Agents, 2002, 2(2), 143-155] and its potential medical uses, mainly in diseases in the central nervous system (CNS), in particular for treatment of neurodegenerative diseases, e.g. Parkinson's disease, Alzheimer's disease, Huntington's disease, peripheral neuropathy, AIDS dementia, and ear injuries such as noise-induced hearing loss [Progress in Medicinal Chemistry (2002), 40, 23-62; Bioorg. Med. Chem. Lett. 2002,12(2), 147-150; Neuroscience, Oxford, 1998, 86(2), 461-472; J. Neurochemistry (2001), 77(3), 849-863; J. Neuroscience (2000), 20(1), 43-50; J. Neurochemistry (2002), 82(6), 1424-1434; Hearing Research, 2002, 166(1-2), 33-43].

The following patent documents relate to Compound I, including its medical use and synthesis: WO 9402488, WO9749406, US 5621100, EP 0651754 and EP 112 932.

By the known methods, Compound I is synthesized in a solid amorphous form. The inventors have now discovered 3 crystalline forms of Compound I (named alpha, beta and gamma) thereby providing an opportunity to improve the manufacturing process of Compound I and its pharmaceutical use. There exists a need for crystalline forms, which may exhibit desirable and beneficial chemical and physical properties. There also exists a need for reliable and reproducible methods for the manufacture, purification, and formulation of Compound I to permit its feasible commercialisation.

## SUMMARY OF THE INVENTION

In a first aspect the present invention relates to a crystalline form of Compound I.

Accordingly, the invention provides a crystalline form of Compound I named alpha and characterized by one or more of: (i) the X-Ray powder diffractogram shown in Figure 1 as measured using CuKα radiation; (ii) the solid state Carbon-13 NMR spectrum shown in Figure 7; (iii) the NIR reflectance spectrum shown in Figure 10.

In a further aspect the invention provides a crystalline form of Compound I named beta and characterized by one or more of: (i) the X-Ray powder diffractogram shown in Figure 2 as measured using CuKα radiation; (ii) the solid state Carbon-13 NMR spectrum shown in Figure 8; (iii) the NIR reflectance spectrum shown in Figure 11.

In a still further aspect the invention provides a crystalline form of Compound I named gamma and characterised by one or more of: (i) the X-Ray powder diffractogram shown in Figure 3 as measured using CuKα radiation; (ii) the solid state Carbon-13 NMR spectrum shown in Figure 9; (iii) the NIR reflectance spectrum shown in Figure 12.

The invention further relates to methods for preparing the crystalline forms of the invention and the use of such forms in the preparation of a medicament comprising Compound I as an active ingredient.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 : Shows an x-ray powder diffractogram of Compound I alpha form.
Figure 2 : Shows an x-ray powder diffractogram of Compound I beta form.
Figure 3 : Shows an x-ray powder diffractogram of Compound I gamma form.
Figure 4 : Shows a DSC thermogram of Compound I alpha form.
Figure 5 : Shows a DSC thermogram of Compound I beta form.
Figure 6 : Shows a DSC thermogram of Compound I gamma form.
Figure 7 : Shows a solid state Carbon-13 NMR spectrum of Compound I alpha form.
Figure 8 : Shows a solid state Carbon-13 NMR spectrum of Compound I beta form.
Figure 9 : Shows a solid state Carbon-13 NMR spectrum of Compound I gamma form.
Figure 10 : Shows a NIR reflectance spectrum of Compound I alpha form.

Figure 11: Shows a NIR reflectance spectrum of Compound I beta form.
Figure 12: Shows a NIR reflectance spectrum of Compound I gamma form.

Further details are revealed in the Examples below.

## DETAILED DESCRIPTION OF THE INVENTION

The discovery of a new crystalline form of a pharmaceutically useful compound provides an opportunity to improve the performance characteristics of the pharmaceutical product and the manufacturing process.

Differences in physical properties, such as stability (shelf-life), bioavailability, solubility, and dissolution rate, exhibited by the different solid forms of a compound are important factors in the manufacturing and formulation of a compound. Differences in stability can result from changes in chemical reactivity (e.g. oxidation) or mechanical changes (e.g. tablets crumble on storage as a kinetically favoured polymorph converts to thermodynamically more stable polymorph) or both. The physical properties of a solid form are important in processing, e.g. one solid form might be more difficult to filter and wash free of impurities. This can be due to differences in particle shape and size distribution between one crystalline form relative to the other and the amorphous form.

Additionally, generally for drugs that exist in polymorphic forms and which are sold in solid form it is important for both medical and commercial reasons to produce and market a known polymorphic form. The discovery of crystalline Compound I and the existence of 3 crystalline polymorphic forms enables the development of a defined crystalline form in place of an amorphous solid. Also, the physical properties of the crystalline Compound I offer advantages for formulation development and tablet preparation, e.g. direct compression is facilitated by having a defined crystal form.

Crystalline compounds are more stable than the corresponding amorphous compound, and this is particularly important in the case of the air sensitive and light sensitive Compound I.

Experiments have been carried out in a Heraeus Suntest CPS+ where the solid compound was exposed to light for 14h at 650W. The light treatment led to almost 60% degradation of the amorphous substance while the crystalline forms showed less than 30% degradation.

Compound I contains two sulphur atoms and is easily oxidised to a complex mixture of sulphones and sulphoxides. This sensitivity to oxidation requires great care during

purification of Compound I. The present invention, which makes purification of Compound I by crystallisation possible, reduces the levels of oxidised compounds as compared to the product obtained when the inventors have used other methods of purification such as chromatography.

In the final step in the synthesis of Compound I, the desired thiol ethyl side chains are introduced using ethyl mercaptan as a reactant [J.Med. Chem. 1997, 40(12), 1863-1869; Curr. Med. Chem. - Central Nervous System Agents, 2002, 2(2), 143-155]. Ethyl mercaptan has a characteristic strong odour, which is undesirable in a pharmaceutical product. The isolation of Compound I as an amorphous solid results in inclusion of ethyl mercaptan in the solid product, while the levels of this undesired reactant is reduced through crystallisation.

Additionally, the physical characteristics of the crystalline forms of the invention improve the isolation step by for example decreasing the filtration times compared to the amorphous form of Compound I, which is of great significance for the large scale manufacturing of Compound I.

A further difference in the physical chemical properties of the crystalline forms compared to the amorphous form is the higher melting points, cf. Table I below, which can give advantages in further processing.

As indicated above the inventors have now discovered that Compound I can be made in a crystalline form and that there is at least 3 crystalline polymorphs of Compound I, herein denominated alpha, beta and gamma.

Thus, in a broad aspect the invention relates to a crystalline form of Compound I. As used herein the expression "a crystalline form of Compound I" comprises any crystalline forms of Compound I, i.e. in contrast to the amorphous form. In particular the term "crystalline Compound I" includes the alpha, beta or gamma crystalline form of Compound I, which forms are as defined herein.

Crystalline forms of a compound are differentiated by the positions of the atomic nuclei in the unit cell of the solidified compound. The differences produce different macroscopic properties like thermal behaviour, vapour permeability and solubility, which as indicated above have practical consequences in pharmacy. The various forms described herein may be distinguishable from one another through the use of various analytical techniques known to one of ordinary skill in the art. Such techniques include, but are not limited to X-ray powder

diffraction (XRD), differential scanning calorimetry (DSC), solid-state nuclear magnetic resonance (NMR) spectroscopy; and Near-infrared (NIR) spectroscopy. Crystalline forms of a compound are most readily distinguished by X-ray analysis. Single crystal X-ray crystallography yields data that can be used to determine the positions of the nuclei, which in turn may be visualized with computer or mechanical models, thus providing a three-dimensional image of the compound. While single crystal X-ray studies provide unmatched structural information, they are expensive and quality data can sometimes be difficult to acquire. Powder X-ray diffraction is used more frequently by the pharmaceutical industry to characterize new crystalline forms of drugs than is single crystal X-ray analysis. Powder X-ray diffraction yields a fingerprint that is unique to the crystalline form and is able to distinguish it from the amorphous compound and all other crystalline forms of the compound.

One embodiment of the invention relates to a crystalline form of Compound I denominated alpha characterized by the X-Ray powder diffractogram shown in Figure 1 as measured using CuKα radiation. The alpha form of Compound I may also be characterized by the solid state Carbon-13 NMR spectrum shown in Figure 7. The alpha form of Compound I may also be characterized by the NIR reflectance spectrum shown in Figure 10. The alpha form of Compound I may also be characterized by having a melting point in the range of 180-190°C. The alpha form of Compound I may also be characterized by having DSC thermogram substantially in accordance with that shown in Figure 4. The alpha form of Compound I may also be characterized by a DSC thermogram having an endotherm from about 170 °C to about 200°C.

A further embodiment relates to a crystalline form of Compound I denominated beta characterized by the X-Ray powder diffractogram shown in Figure 2 as measured using CuKα radiation. The beta form of Compound I may also be characterized by the solid state Carbon-13 NMR spectrum shown in Figure 8. The beta form of Compound I may also be characterized by the NIR reflectance spectrum shown in Figure 11. The beta form of Compound I may also be characterized by having a melting point in the range of 209-213°C, preferably about 211°C. The beta form of Compound I may also be characterized by having DSC thermogram substantially in accordance with that shown in Figure 5. The beta form of Compound I may also be characterized by a DSC thermogram having an endotherm from about 205°C to about 220°C.

A further embodiment relates to a crystalline form of Compound I denominated gamma characterized by the X-Ray powder diffractogram shown in Figure 3 as measured using CuKα radiation. The gamma form of Compound I may also be characterized by the solid state Carbon-13 NMR spectrum shown in Figure 9. The gamma form of Compound I may also be characterized by the NIR reflectance spectrum shown in Figure 12. The gamma form of Compound I may also be characterized by having a melting point in the range of 212-218°C. The gamma form of Compound I may also be characterized by having DSC thermogram substantially in accordance with that shown in Figure 6. The gamma form of Compound I may also be characterized by a DSC thermogram having an endotherm from about 210°C to about 225°C.

The invention also relates to any mixtures of the crystalline forms of the invention, e.g. a mixture of the alpha and gamma crystalline form of Compound I.

As used herein by expressions like "crystalline form of Compound I characterized by the X-Ray powder diffractogram shown in Figure (1) as measured using CuKα" is meant the crystalline form of Compound I (named alpha) having an X-ray powder diffractogram substantially similar to Figure 1, i.e. exhibiting an X-ray powder diffraction pattern as exemplified in that Figure and measured under comparable conditions as described in Example 5.1 or by any comparable method using CuKα radiation. This definition also applies mutatis mutandis to the NMR and NIR Figures and for all of the three polymorphs identified, i.e. alpha, beta and gamma, respectively, such that margins of analytical variations are taken into consideration. The solid state Carbon-13 NMR spectra referred to herein are preferably measured using a sample spinning speed of 5000Hz on a spectrometer with a CP-MAS probe. Thus, the NMR spectrum is preferably provided as described in Example 5.2 or by any comparable method and the NIR reflectance spectra referred to herein are preferably provided as described in Example 5.3 or by any comparable method, in particular with a resolution $2cm^{-1}$ and correction of baseline shift and slope with Multiplicative Scatter Correction (MSC).

In a preferred embodiment, the crystalline form of the invention is having an elemental composition corresponding to Compound I after correction of water content, i.e. an elemental composition which after correction of water content is in the range of 6.82±0.4%N, 64.37±0.4%C, 5.40±0.4%H. In particular in one embodiment, the alpha, beta or gamma forms as described herein are further characterised by having an elemental

composition corresponding to Compound I, i.e. after correction of water content, which is in the range of 6.82±0.4%N, 64.37±0.4%C, 5.40±0.4%H.

In further embodiments, the invention relates to a crystalline form of Compound I, which is substantially pure. The term "substantially pure", as used herein, means that the crystalline form of Compound I, e.g. the alpha, beta or gamma form, is having a purity of at least about 90% including, e.g., at least about 93%, and at least about 95%.

The amorphous form of Compound I has a melting point about 150°C which is easy to distinguish from the melting points of the herein described crystalline form of Compound I, cf. Table 1 in Example 7. Accordingly, within the invention is also crystalline forms of Compound I having a melting point which is at least 175°C, or at least 180°C, such as in the range of 175°C- 225°C, 180°C- 220°C, or 181°C-218°C.

By the term "melting point" as used herein is meant the onset value of the melting endotherm as measured by DSC, cf. Example 5.4. The melting point for the amorphous form of Compound I may also be termed glass transition temperature ($T_g$).

In a further aspect, the invention relates to solid Compound I consisting mainly of crystalline Compound I (e.g. the crystalline alpha, beta or gamma form as defined herein or any mixtures hereof) as compared to the amorphous form of Compound I. The term "mainly " in this context means that the a relatively minor portion of amorphous Compound I may be present in the solid Compound I, such as, e.g. at most 25%, or at most 20% (w/w), or at most 10% (w/w) or at most 5% (w/w) of the solid compound I is amorphous. Within the meaning of "a solid Compound I consisting mainly of crystalline Compound I" is also included solid Compound I where essentially no amorphous Compound I is present.

The invention also relates to solid Compound I having a melting point which is significantly higher than the melting point of amorphous Compound I, e.g. in the range of 175-225°C, 180°C- 220°C, or 181°C-218°C. Within the invention is also solid Compound I characterised by one or more of: (i) a DSC thermogram having an endotherm from about 170 °C to about 200°C; (ii) a DSC thermogram having an endotherm from about 205°C to about 220°C; (iii) a DSC thermogram having an endotherm from about 210°C to about 225°C.

The invention also relates to a solid Compound I as described above consisting mainly of the crystalline alpha form Compound I described herein. The term "mainly" in the present

context means that the solid Compound I consist of at least 75%, such as at least 80%, at least 90%, or at least 95% crystalline alpha form of the total Compound I present. This solid may further be characterised by one or more of: a melting point in the range of 180-190°C; a DSC thermogram substantially in accordance with that shown in Figure 4; a DSC thermogram having an endotherm from about 170 °C to about 200°C.

The invention also relates to a solid Compound I as described above consisting mainly of the crystalline beta form Compound I described herein. The term "mainly" in the present context means that the solid Compound I consist of at least 75%, such as at least 80%, at least 90%, or at least 95% crystalline beta form of the total Compound I present. This solid may further be characterised by one or more of: a melting point in the range of 209-213°C; a melting point about 211°C; by a DSC thermogram substantially in accordance with that shown in Figure 5; a DSC thermogram having an endotherm from about 205°C to about 220°C.

The invention also relates to a solid Compound I as described above consisting mainly of the crystalline gamma form Compound I described herein. The term "mainly" in the present context means that the solid Compound I consist of at least 75%, such as at least 80%, at least 90%, or at least 95% crystalline gamma form of the total Compound I present. This solid may further be characterised by one or more of: a melting point in the range of 212-218°C; a DSC thermogram substantially in accordance with that shown in Figure 6; a DSC thermogram having an endotherm from about 210°C to about 225°C.

Broadly speaking, the novel crystalline forms of Compound I may be prepared by a variety of methods, including but not limited to crystallizing Compound I from a suitable solvent. Compound I may be prepared using methods known in the art, such as those described herein. By way of general guidance, Compound I may be mixed with a suitable solvent which may be heated to facilitate the dissolution of Compound I. The combination of solvent and Compound I may be heated to facilitate dissolution of the compound in the solvent, as well as assisting the subsequent conversion to the crystalline form. Preferred temperatures in this regard may range from about 30°C to about the boiling point (i.e., the reflux temperature) of the solvent. More preferred temperatures may range from about 60°C to about the boiling point of the solvent. The resulting mixture of solvent and Compound I may be cooled to initiate and/or continue crystallization. The mixture is preferably cooled

(i.e. including natural cooling to ambient temperature) to a temperature which ranges from, e.g., about minus 20°C to about 20°C, e.g. to ambient temperature. The precipitated solids may be isolated from the cooled mixture by for example filtration or centrifugation, and if necessary washed with a suitable solvent such as, but not limited to, the solvent employed for the crystallization, and dried *in vacuo* at ambient or slightly elevated temperature, e.g. under a nitrogen purge.

The invention in one aspect relates to a process for preparing the crystalline alpha form of Compound I as defined herein, which process comprises the steps of: (a) dissolving Compound I in an alcohol, (b) crystallizing by precipitation Compound I from the alcohol, and (c) separating the alcohol from the obtained crystalline alpha form of Compound I; or alternatively by a process comprising the steps of: (a) suspending Compound I in an alcohol for a period of time sufficient to convert it into the crystalline alpha form, and (b) separating the alcohol from the obtained crystalline alpha form of Compound I. In a preferred embodiment, the alcohol is a $C_{1-6}$ aliphatic alcohol, preferably methanol.

The invention in a further aspect relates to a process for preparing the crystalline beta form of Compound I as defined herein, which process comprises the steps of: (a) dissolving Compound I in a carboxylic aliphatic ester, (b) crystallizing by precipitation Compound I from the carboxylic aliphatic ester, and (c) separating the carboxylic aliphatic ester from the obtained crystalline beta form of Compound I; or alternatively by a process comprising the steps of: (a) suspending Compound I in a carboxylic aliphatic ester for a period of time sufficient to convert it into the crystalline beta form, and (b) separating the carboxylic aliphatic ester from the obtained crystalline beta form of Compound I. In a preferred embodiment, the carboxylic aliphatic ester is a $C_{1-6}$ carboxylic aliphatic ester, preferably isopropyl acetate.

In a further aspect the invention relates to a process for preparing the crystalline gamma form of Compound I as defined herein, which process comprises the steps of: (a) dissolving Compound I in a nitrile, preferably an aliphatic nitrile, (b) crystallizing by precipitation Compound I from the nitrile, and (c) separating the nitrile from the obtained crystalline gamma form of Compound I; or alternatively by a process comprising the steps of: (a) suspending Compound I in a nitrile, preferably an aliphatic nitrile, for a period of time sufficient to convert it into the crystalline gamma form, and (b) separating the nitrile from

the obtained crystalline gamma form of Compound I. In a preferred embodiment the nitrile is a $C_{1-6}$ aliphatic nitrile, preferably acetonitrile.

Seed crystals may be added to any crystallization mixture to promote crystallization.

It has also been found that each of the crystalline form alpha and beta can be converted to the crystalline gamma form, in the presence of a liquid, in particular acetonitrile as shown in Example 4.1.

The invention also relates to a crystalline product, in particular the crystalline forms of Compound I obtainable, or in a preferred embodiment obtained, by a process described herein for the preparation of Crystalline Compound I.

The invention in a further aspect relates to a process for the preparation of Compound I comprising converting a crystalline form of Compound I (e.g. the alpha, beta or gamma form as described herein or any mixtures hereof) into the amorphous form of Compound I. Such process in a preferred embodiment comprises the steps of: (a) dissolving crystalline Compound I in an aromatic solvent, i.e. an aromatic hydrocarbon, preferably an alkyl-benzene such as xylene or toluene, (b) precipitating Compound I from the aromatic solvent; and (c) separating the aromatic solvent from the precipitated amorphous Compound I.

As indicated above the formation of crystalline Compound I is very useful as a purification step in the manufacturing of Compound I for pharmaceutical use. Accordingly, the invention in one aspect relates to a process for the preparation of Compound I comprising a crystallization step as described herein.

The invention further relates to the use of a crystalline Compound I or a solid of the invention in the preparation of a medicament comprising Compound I as an active ingredient.

Within the invention is also a pharmaceutical composition comprising an effective amount of a crystalline Compound I as described herein, in particular the alpha, beta or gamma forms defined herein or mixtures thereof, and a pharmaceutically acceptable carrier.

The crystalline product of the invention, in particular the alpha, beta or gamma crystalline forms, or mixtures thereof, can be used in the preparation of a pharmaceutical composition with Compound I in solution, e.g. a composition similar to those disclosed in US 6,200,968.

Alternatively, the crystalline product of the invention, i.e. including the crystalline alpha, beta or gamma form, or mixtures thereof, may be formulated into a variety of pharmaceutical compositions. Examples of such formulations comprising a crystalline product of the invention (e.g. crystalline alpha, beta or gamma forms) are tablets, capsules, granules, powders, suppositories and suspensions. The expression "crystalline product of the invention" means a crystalline Compound I or a solid Compound I as described herein, i.e. by "solid Compound I" is in the present context understood a solid Compound I consisting mainly of crystalline Compound I as compared to amorphous Compound.

In one embodiment, the pharmaceutical compositions of the invention comprise Compound I mainly or only in one of the following forms: the crystalline alpha, beta or gamma form. In another embodiment, the pharmaceutical composition may also comprise solid amorphous Compound I in addition to the one or more crystalline forms described herein.

The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other adjuvants and excipients, e.g. in accordance with techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

In an embodiment of the pharmaceutical composition, Compound I is administered in an amount of from about 0.001 to about 100 mg/kg body weight per day. Compound I may, e.g. be administered in a unit dosage form containing said compound in an amount of about 0.01 to 100 mg. The total daily dose is, e.g., in the range of about 0.05 - 500 mg. The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.01 to about 1000 mg, preferably from about 0.05 to about 500 mg. For parenteral routes such as intravenous, intrathecal,

intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

As indicated above, the following embodiments are within the invention: Crystalline Compound I for use as a medicament; the crystalline alpha form for use as a medicament; the crystalline beta form for use as a medicament; and the crystalline gamma form for use as a medicament.

The invention further relates to the use of a crystalline Compound I as described herein, e.g. the alpha, beta or gamma form defined herein or mixtures thereof, in the preparation of a medicament for the treatment of a CNS disease, e.g. for treatment of a neurodegenerative disease, such as e.g. Parkinson's disease, Alzheimer's disease, Huntington's disease, peripheral neuropathy, AIDS dementia, or ear injuries including noise-induced hearing loss.

Similarly, within the invention is also a method for treating a neurodegenerative disease, such as e.g. Parkinson's disease, Alzheimer's disease, Huntington's disease, peripheral neuropathy, AIDS dementia, or ear injuries including noise-induced hearing loss, comprising administering a pharmaceutically effective amount of a crystalline Compound I as described herein, e.g. the alpha, beta or gamma form defined herein or mixtures thereof.

The term "treatment" in connection with a disease as used herein also includes prevention as the case may be. The term "disease" as used herein also includes a disorder as the case may be.

The invention disclosed herein is further illustrated by the following non-limiting examples.

**EXAMPLES**

In the following Examples 1-3 the starting material "amorphous Compound I" may be prepared as described by Kaneko M. et al in J. Med. Chem. 1997, 40, 1863-1869.

**Example 1. Preparation of crystalline alpha form of Compound I**

Method I):

6,0 g amorphous Compound I was dissolved in 30 ml acetone. 0,6 g potassium carbonate was added and the suspension was stirred at room temperature for 1 hour before it was filtered to remove potential minor insoluble impurities and inorganic salts. The filter cake was washed with acetone. The filtrate was then evaporated on a rotary evaporator under reduced pressure at 60°C to a final volume of 10 ml to which 100 ml methanol was added

slowly. The product separated as an oil, which almost dissolved on heating to reflux. Subsequently the residual insoluble impurities were removed by filtration. The filtrate was left with stirring at room temperature. A solid separated and was isolated by filtration. The filter cake was washed with methanol and dried in vacuo at 60°C overnight.

Yield 2,83 g (47%), mp=182.4°C (DSC onset value), Weight loss by heating: 0.5%, Elemental analysis: 6.71%N, 63.93%C, 5.48%H, theoretical values corrected for 0.5% $H_2O$: 6.79%N, 64.05%C, 5.43%H, Purity (HPLC, area%): 97.4

Method II):

5 g amorphous Compound I was dissolved in 25 ml acetone by gentle heating. 10 ml Methanol was added very slowly until the solution got turbid. The solution was allowed to cool to room temperature by natural cooling. The suspension was filtered and the filter-cake discarded. During filtration more material precipitated in the filtrate. The filtrate was heated until all material redissolves. Cold methanol was then added to the solution until precipitation was observed. The slightly turbid solution was then heated until all material was in solution. The solution was allowed to cool to room temperature, and the precipitate was removed by filtration. The second filter-cake was discarded. During the filtration some material separated in the filtrate. Heating redissolved the beginning crystallisation in the filtrate. Cold methanol was then added to the solution until precipitation was observed. The suspension was heated until a clear solution was obtained. The solution was allowed to reach room temperature by natural cooling. After a short period of time (15 min) precipitation begun. The precipitated pale yellow product was isolated by filtration and dried in vacuo at 50°C overnight.

mp=188.9°C (DSC onset value), Weight loss by heating: 0.3%, Elemental analysis: 6.53%N, 64.33%C, 5.43%H, theoretical values: 6.82%N, 64.37%C, 5.37%H, Purity (HPLC, area%): 97,6%.

**Example 2. Preparation of crystalline beta form of Compound I**

28,0 g amorphous Compound I was dissolved in 250 ml tetrahydrofuran (THF) and evaporated onto 60 g silica gel. The compound was purified by column chromatography on silica gel (Ø: 10 cm h: 5 cm with 2,7 l THF/heptane 2/1). The eluent containing the desired compound was evaporated a rotary evaporator at reduced pressure at 50°C to a solid (26 g). The solid was suspended in 600 ml isopropyl acetate and the suspension heated to reflux until almost all material was dissolved. The suspension was cooled on a water/ice bath. The

cold suspension was filtered, and the filter cake was washed with isopropyl acetate and dried in vacuo overnight at 50°C.

Yield: 16,9 g (61%), mp=211.7°C (DSC onset value), Weight loss by heating: 0.2%, Elemental analysis: 6.59%N, 64.63%C, 5.41%H, theoretical values: 6.82%N, 64.37%C, 5.40%H, Purity (HPLC, area%): 98.2

**Example 3. Preparation of crystalline gamma form of Compound I**

15 g amorphous Compound I was dissolved in 75 ml acetone. 1.5 g potassium carbonate was added and the suspension stirred for 90 minutes. The suspension was filtered. The filtrate was reduced to approximately 30 ml on a rotary evaporator at reduced pressure at 60°C. 150 ml Methanol was added to the reduced filtrate, and some sticky material separated. The suspension was heated to reflux. During the heating all material dissolves. The solution was allowed to cool to room temperature by natural cooling, during this period solid material separated. The suspension was left with stirring at room temperature overnight.

The suspension was filtered and the filter cake washed with methanol. The filter cake was dried in vacuo at 50°C overnight. Intermediate yield is 10,2 gram (68%).

The dry filter cake was suspended in 100 ml acetonitrile (ACN) and heated to reflux. At reflux a turbid solution was obtained. Additional acetonitrile was added until a clear solution was obtained; in total the filter cake was dissolved in 200 ml acetonitrile including the 100 ml used for suspension.

The solution was cooled to room temperature overnight. The following day the crystalline product was isolated by filtration. The filter cake was washed by a small amount of acetonitrile and dried in vacuo at 55°C overnight.

Yield: 6,17 g, 41%, mp=218.0°C (DSC onset value), Weight loss by heating: <0.1%, Elemental analysis: 6.80%N, 64.38%C, 5.43%H, theoretical values: 6.82%N, 64.37%C, 5.40%H, Purity (HPLC, area%): 98.6

**Example 4 Transformation between different solid forms of Compound I**

**4.1 Conversions to crystalline Compound I**

In the following examples are used excess of solid Compound I, i.e. compared to the solvent the amounts of solid Compound I is such that not all the solid material comes into solution. The amounts used varied between 25-50 mg solid Compound I and 2-5 ml solvent. By

"solid Compound I" is in the present context meant amorphous Compound I or any of the crystalline forms of Compound I as indicated below.

(i) Excess of amorphous Compound I was added to methanol and the resulting suspension was stored on a rotarmix for 4 days at room temperature. After 4 days the solid was the alpha form as determined by powder X-ray diffraction.

(ii) Excess of the crystalline alpha form of Compound I was added to methanol and the resulting suspension was stored on a rotarmix for 4 days at room temperature. After 4 days the solid was still the alpha form as determined by powder X-ray diffraction.

(iii) Excess of the crystalline beta form of Compound I was added to methanol and the resulting suspension was stored on a rotarmix for 4 days at room temperature. After 4 days the solid was the alpha form as determined by powder X-ray diffraction.

(iv) Excess of the crystalline gamma form of Compound I was added to methanol and the resulting suspension was stored on a rotarmix for 4 days at room temperature. After 4 days the solid was still the gamma form as determined by powder X-ray diffraction.

(v) Excess of a 1:1 mixture of the alpha and the gamma form of Compound I was added to methanol and the resulting suspension was on a rotarmix stored for 4 days at room temperature. After 4 days the major part of the solid was the gamma form. After filtration the supernatant was left for evaporation of the solvent. The resulting solid was the alpha form as determined by powder X-ray diffraction.

(vi) Excess of amorphous Compound I was added to acetonitrile (ACN) and the resulting suspension was stored on a rotarmix for 4 days at room temperature. After 4 days the solid was the gamma form as determined by powder X-ray diffraction.

(vii) Excess of the crystalline alpha form of Compound I was added to ACN and the resulting suspension was stored on a rotarmix for 4 days at room temperature. After 4 days the solid was the gamma form as determined by powder X-ray diffraction.

(viii) Excess of the crystalline beta form of Compound I was added to ACN and the resulting suspension was stored on a rotarmix for 4 days at room temperature. After 4 days the solid was the gamma form as determined by powder X-ray diffraction.

(ix) Excess of the crystalline gamma form of Compound I was added to ACN and the resulting suspension was stored on a rotarmix for 4 days at room temperature. After 4 days the solid was still the gamma form as determined by powder X-ray diffraction.

Conclusion:

Amorphous Compound I and the crystalline beta form can be converted into crystalline alpha form in a methanol suspension.

Amorphous Compound I, the crystalline alpha form and the crystalline beta form can be converted into the crystalline gamma form by suspension of excess of the solid material in acetonitrile.

**4. 2 Conversions from the crystalline alpha form of Compound I to the amorphous form.**

15 g crystalline alpha form of Compound I was heated to reflux in a mixture of Toluene (110 mL) and methanol (1 mL); a clear solution was obtained. Under reduced pressure the solvent volume was decreased by 10 mL and the solution was cooled overnight in a freezer. The resulting solid was isolated by filtration, dried in vacuo over two days at 40°C to give 13.2 g of a solid. The melting temperature of the solid was approx. 150°C which characterises the amorphous form of Compound I as compared to the crystalline forms, cf. Table 1 below.

**Example 5 Analytical methods**

(5.1) XRPD patterns were measured on a Diffractometer under the following conditions:
Radiation: Cu(Kα1), germanium monochromator, λ=1.540598 Å
Position Sensitive Detector (PSD) covering 7°
Scan type: Step scan, steps: 0.1°, 125-150 sec. pr. step
Range: 5-45°2θ
Sample measuring method: Transmission

(5.2) The solid state NMR was performed under the following conditions:
The Carbon-13 CP/MAS (cross-polarization / magic-angle spinning) NMR spectra were acquired at room temperature at 11.75 Tesla on a Bruker Avance DRX-500 spectrometer equipped with a 4 mm CP/MAS probe. The sample spinning speed was 5000Hz, and 10240 scans were acquired using a recycle delay of 5 sec. For the cross polarization, spin-lock radio frequency fields of 50 kHz and a contact time of 5 msec were employed.

(5.3) Near-infrared (NIR) data were collected with Bomem MB 160 FT/NIR spectrometer with Powder SamplIR. The NIR reflectance spectra were recorded between 14.000-4.000cm-1 with resolution 2cm-1 (16 scans, high gain). Baseline shift and slope in

NIR spectra, which is often seen in powder, were removed with Multiplicative Scatter Correction (MSC).

(5.4) Melting points were determined on a DSC (Differential Scanning Calorimeter) as the onset temperature of the melting endotherm. About 2 mg of sample was heated in an aluminium crucible with loose lid, at 5°C/min under $N_2$ flow.

**Example 6. Analytical results of Example 1 (method I), Example 2 and Example 3.**

- All crystalline forms have elemental compositions corresponding to Compound I, after correction for water content, i.e. 6.82±0.4%N, 64.37±0.4%C, 5.40±0.4%H.
- The X-ray powder diffractogram of the alpha form (XRPD) is shown in Figure 1.
- The X-ray powder diffractogram of the beta form (XRPD) is shown in Figure 2.
- The X-ray powder diffractogram of the gamma form (XRPD) is shown in Figure 3.
- The DSC thermograms are shown in Figures 4-6 (alpha form in Figure 4; beta form in Figure 5; and gamma form in Figure 6).
- The solid state NMR spectra are shown in Figure 7 for the alpha form, Figure 8 for the beta form and Figure 9 for the gamma form.
- The NIR-spectra are shown in Figure 10 for the alpha form, Figure 11 for the beta form and Figure 12 for the gamma form.

**Example 7 Melting points**

The melting points (cf. Example 5.4 above) obtained for the amorphous, alpha, beta and gamma solid form of Compound I are shown in Table 1 below.

**Table 1**

| Form | Approx. melting temperature: |
|---|---|
| Amorphous | approx.150°C |
| α | 181-189°C |
| β | approx. 211°C |
| γ | 212-218°C |

## CLAIMS

1. A crystalline form of Compound I.

2. The crystalline form of claim 1, characterized by one or more of:

(i) the X-Ray powder diffractogram shown in Figure 1 as measured using CuKα radiation;

(ii) the solid state Carbon-13 NMR spectrum shown in Figure 7;

(iii) the NIR reflectance spectrum shown in Figure 10.

3. The crystalline form of claim 1, characterized by the X-Ray powder diffractogram shown in Figure 1 as measured using CuKα radiation.

4. The crystalline form of claim 2 or 3 denominated as the alpha form of Compound I.

5. The crystalline form of claim 1, characterized by one or more of:

(i) the X-Ray powder diffractogram shown in Figure 2 as measured using CuKα radiation;

(ii) the solid state Carbon-13 NMR spectrum shown in Figure 8;

(iii) the NIR reflectance spectrum shown in Figure 11.

6. The crystalline form of claim 1, characterized by the X-Ray powder diffractogram shown in Figure 2 as measured using CuKα radiation.

7. The crystalline form of claim 5 or 6 denominated as the beta form of Compound I.

8. The crystalline form of claim 1, characterized by one or more of:

(i) the X-Ray powder diffractogram shown in Figure 3 as measured using CuKα radiation;

(ii) the solid state Carbon-13 NMR spectrum shown in Figure 9;

(iii) the NIR reflectance spectrum shown in Figure 12.

9. The crystalline form of claim 1, characterized by the X-Ray powder diffractogram shown in Figure 3 as measured using CuKα radiation.

10. The crystalline form of claim 8 or 9 denominated as the gamma form of Compound I.

11. The crystalline form of any of claims 1-10, wherein said form has an elemental composition corresponding to Compound I after correction of water content.

12. The crystalline form of claim 11, wherein said elemental composition is 6.82±0.4%N, 64.37±0.4%C, 5.40±0.4%H.

13. The crystalline form of any of claims 1-12, which is substantially pure.

14. Solid Compound I consisting mainly of crystalline Compound I as compared to the amorphous form of said compound.

15. The solid of claim 14, wherein said crystalline Compound I is the crystalline alpha form defined in claim 4.

16. The solid of claim 14, wherein said crystalline Compound I is the crystalline beta form defined in claim 7.

17. The solid of claim 14, wherein said crystalline Compound I is the crystalline gamma form defined in claim 10.

18. The solid of any of claims 14-17 having a melting point in the range of 175-225°C.

19. The solid of claim 15 having a melting point in the range of 180-190°C.

20. The solid of claim 15 which is characterized by a DSC thermogram having an endotherm from about 170 °C to about 200°C.

21. The solid of claim 16 having a melting point in the range of 209-213°C.

22 The solid of claim 16 which is characterized by a DSC thermogram having an endotherm from about 205°C to about 220°C.

23. The solid of claim 17 having a melting point in the range of 212-218°C.

24. The solid of claim 17 which is characterized by a DSC thermogram having an endotherm from about 210°C to about 225°C.

25. A process for preparing the crystalline alpha form of Compound I comprising the steps of:

a) dissolving Compound I in an alcohol;

b) crystallizing by precipitation Compound I from the alcohol; and

c) separating the alcohol from the obtained crystalline alpha form of Compound I, wherein said alpha form is as defined in claim 2 or 3, optionally in combination with any of claims 11-13.

26. A process for preparing the crystalline alpha form of Compound I comprising the steps of:

a) suspending Compound I in an alcohol for a period of time sufficient to convert it into the crystalline alpha form, and

b) separating the alcohol from the obtained crystalline alpha form of Compound I, wherein said alpha form is as defined in claim 2 or 3, optionally in combination with any of claims 11-13.

27. The process of claim 25 or 26, wherein said alcohol is a $C_{1-6}$ aliphatic alcohol.

28. The process of claim 27, wherein said alcohol is methanol.

29. A process for preparing the crystalline beta form of Compound I comprising the steps of:

a) dissolving Compound I in a carboxylic aliphatic ester.

b) crystallizing by precipitation Compound I from the carboxylic aliphatic ester; and

c) separating the carboxylic aliphatic ester from the obtained crystalline beta form of Compound I,

wherein said beta form is as defined in claim 5 or 6, optionally in combination with any of claims 11-13.

30. A process for preparing the crystalline beta form of Compound I comprising the steps of:

a) suspending Compound I in a carboxylic aliphatic ester for a period of time sufficient to convert it into the crystalline beta form, and

b) separating the carboxylic aliphatic ester from the obtained crystalline beta form of Compound I,

wherein said beta form is as defined in claim 5 or 6, optionally in combination with any of claims 11-13.

31. The process of claim 29 or 30, wherein said carboxylic aliphatic ester is a $C_{1-6}$ carboxylic aliphatic ester.

32. The process of claim 31, wherein said $C_{1-6}$ carboxylic aliphatic ester is isopropyl acetate.

33. A process for preparing the crystalline gamma form of Compound I comprising the steps of:

a) dissolving Compound I in a nitrile, preferably an aliphatic nitrile;

b) crystallizing by precipitation Compound I from the nitrile; and

c) separating the nitrile from the obtained crystalline gamma form of Compound I,

wherein said gamma form is as defined in claim 8 or 9, optionally in combination with any of claims 11-13.

34. A process for preparing the crystalline gamma form of Compound I comprising the steps of:

a) suspending Compound I in a nitrile, preferably an aliphatic nitrile, for a period of time sufficient to convert it into the crystalline gamma form, and

b) separating the nitrile from the obtained crystalline gamma form of Compound I, wherein said gamma form is as defined in claim 8 or 9, optionally in combination with any of claims 11-13.

35. The process of claim 33 or 34, wherein said nitrile is a $C_{1-6}$ aliphatic nitrile.

36. The process of claim 35, wherein said nitrile is acetonitrile.

37. Crystalline Compound I obtainable by a process as described in any of claims 25-36.

38. A process for the preparation of amorphous Compound I comprising the step of converting a crystalline form of Compound I into the amorphous form of Compound I, wherein said crystalline form is as defined in any of claims 1-24.

39. The process of claim 38, wherein said crystalline form is the crystalline alpha form.

40. The process claim 38 or 39 comprising the steps of:

a) dissolving crystalline Compound I in an aromatic solvent;

b) precipitating Compound I from the aromatic solvent; and

c) separating the aromatic solvent from the precipitated amorphous Compound I.

41. The process of claim 40, wherein the aromatic solvent is xylene or toluene.

42. Use of a Crystalline Compound I as defined in any of claims 1-13 or a solid as defined in any of claims 14-24 in the preparation of a medicament comprising Compound I as an active ingredient.

43. A Crystalline Compound I as defined in any of claims 1-13 for use in the preparation of a medicament.

44. A pharmaceutical composition comprising an effective amount of the crystalline Compound I defined in any of claims 1-13 and a pharmaceutically acceptable carrier.

45. Use of the crystalline Compound I defined in any of claims 1-13 in the preparation of a medicament for the treatment of a CNS disease, e.g. for treatment of a neurodegenerative disease.

46. Use of the crystalline Compound I defined in any of claims 1-13 in the preparation of a medicament for the treatment of Parkinson's disease, Alzheimer's disease, Huntington's disease, peripheral neuropathy, AIDS dementia, or ear injuries including noise-induced hearing loss.

47. Use of the crystalline Compound I defined in any of claims 1-13 in the preparation of a medicament for the treatment of Parkinson's disease.

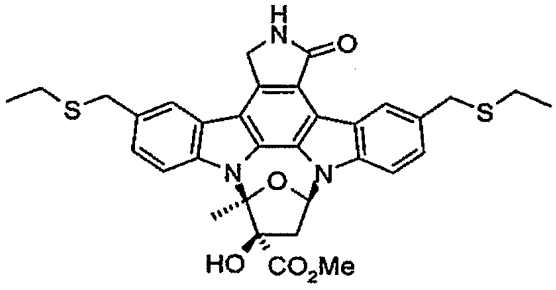
48. A method of treating a neurodegenerative disease comprising administering a pharmaceutically effective amount of the crystalline Compound I defined in any of claims 1-13.

49. A method of treating a disease selected from the group consisting of Parkinson's disease, Alzheimer's disease, Huntington's disease, peripheral neuropathy, AIDS dementia, or ear injuries including noise-induced hearing loss, comprising administering a pharmaceutically effective amount of the crystalline Compound I defined in any of claims 1-13.

50. A method of treating Parkinson's disease comprising administering a pharmaceutically effective amount of the crystalline Compound I defined in any of claims 1-13.

## ABSTRACT

Described are crystalline forms of the compound with the following structure:




as well as methods for their use and preparation.

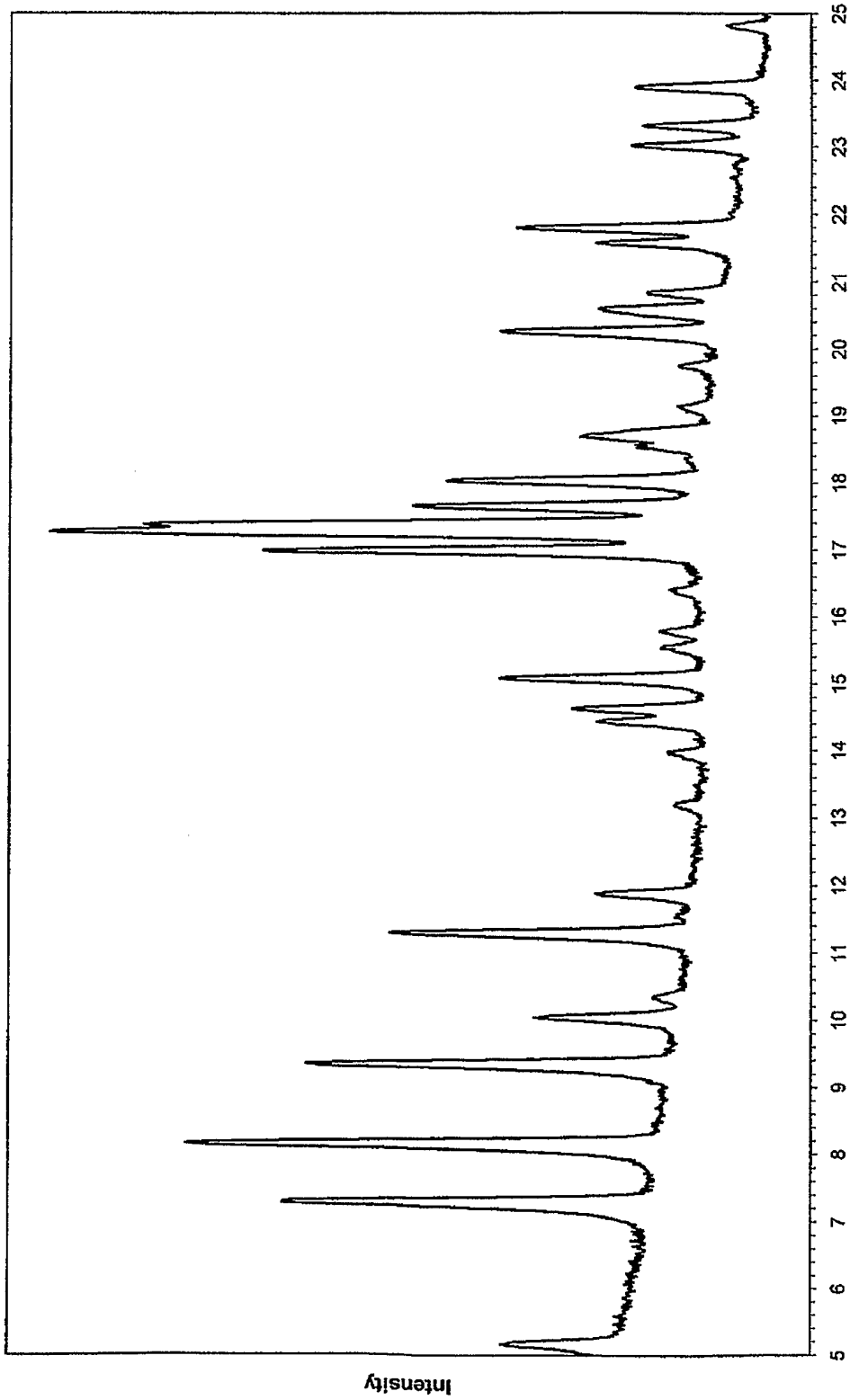



Fig. 1

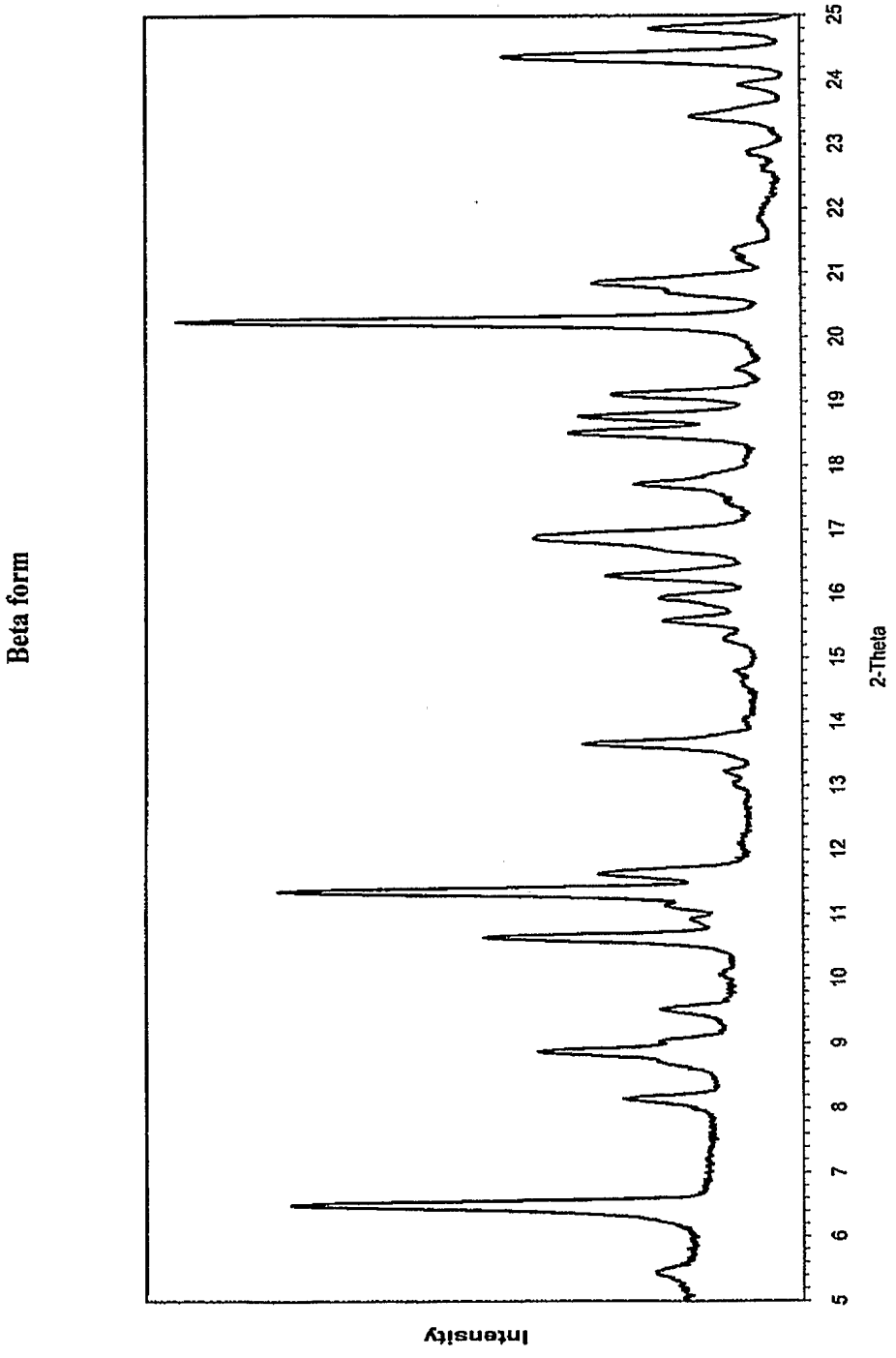



Fig. 2

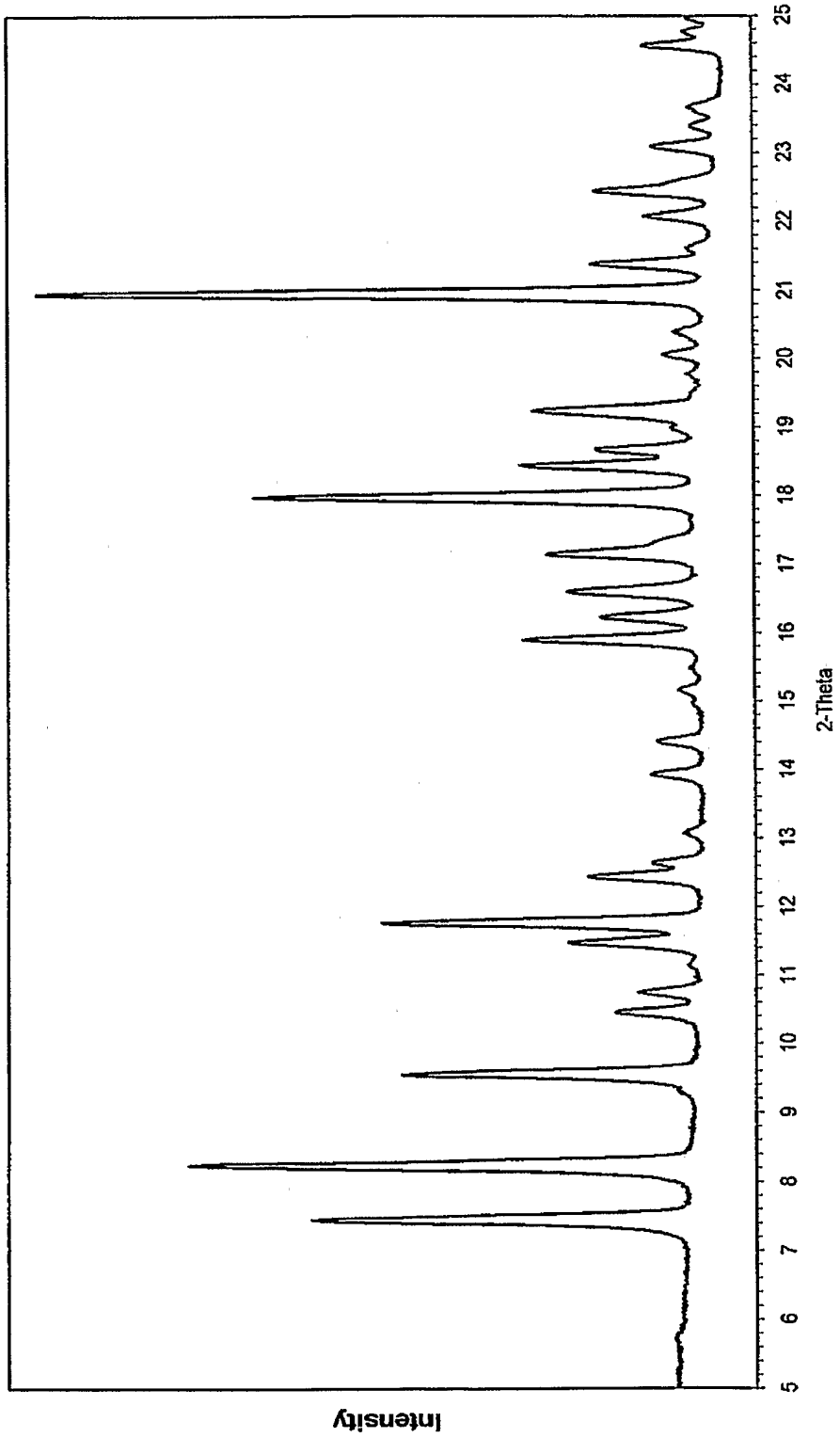



Fig. 3

Alpha form

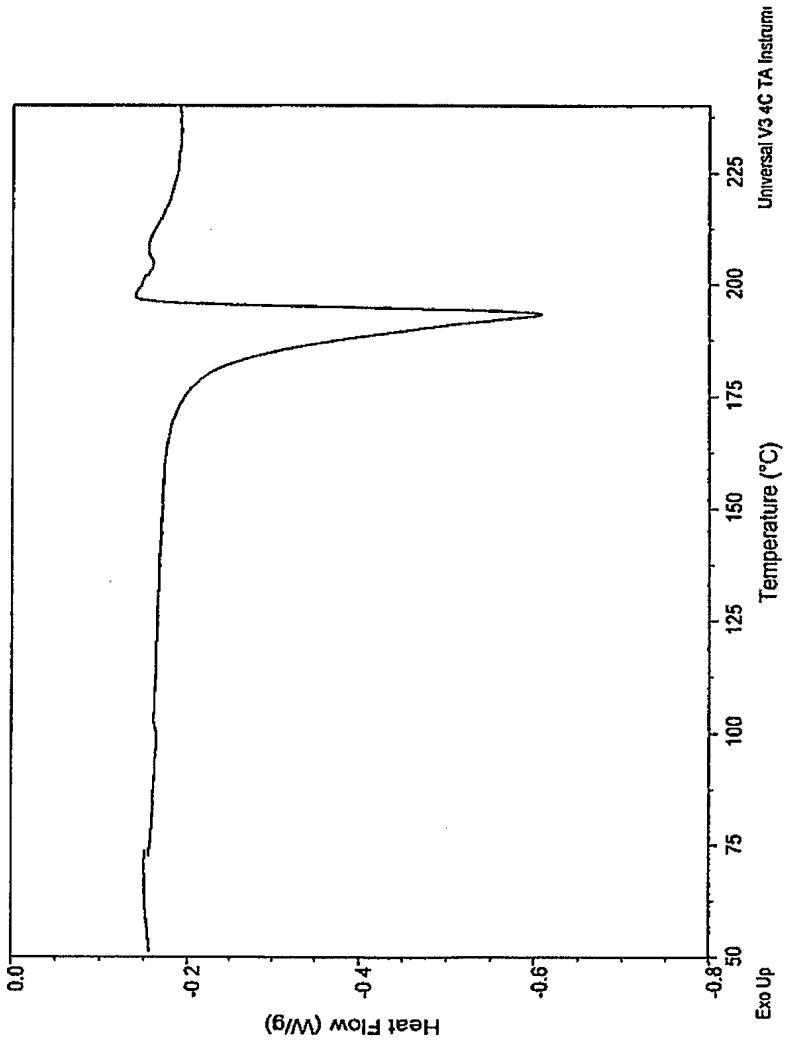



Fig. 4

Beta form

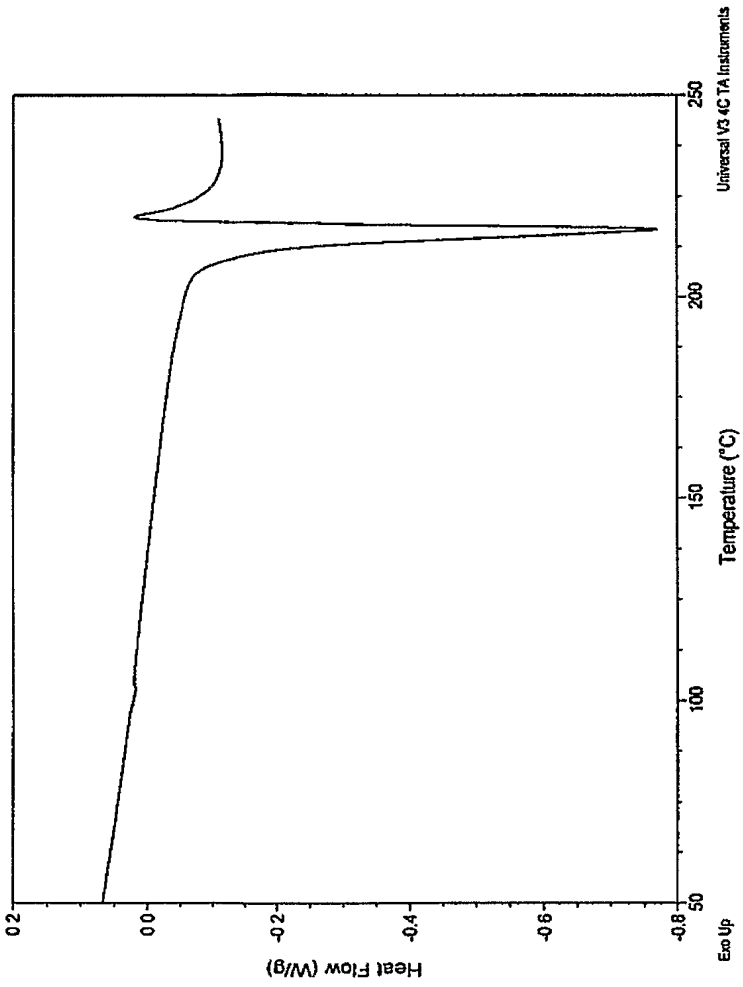



Fig. 5

Gamma form

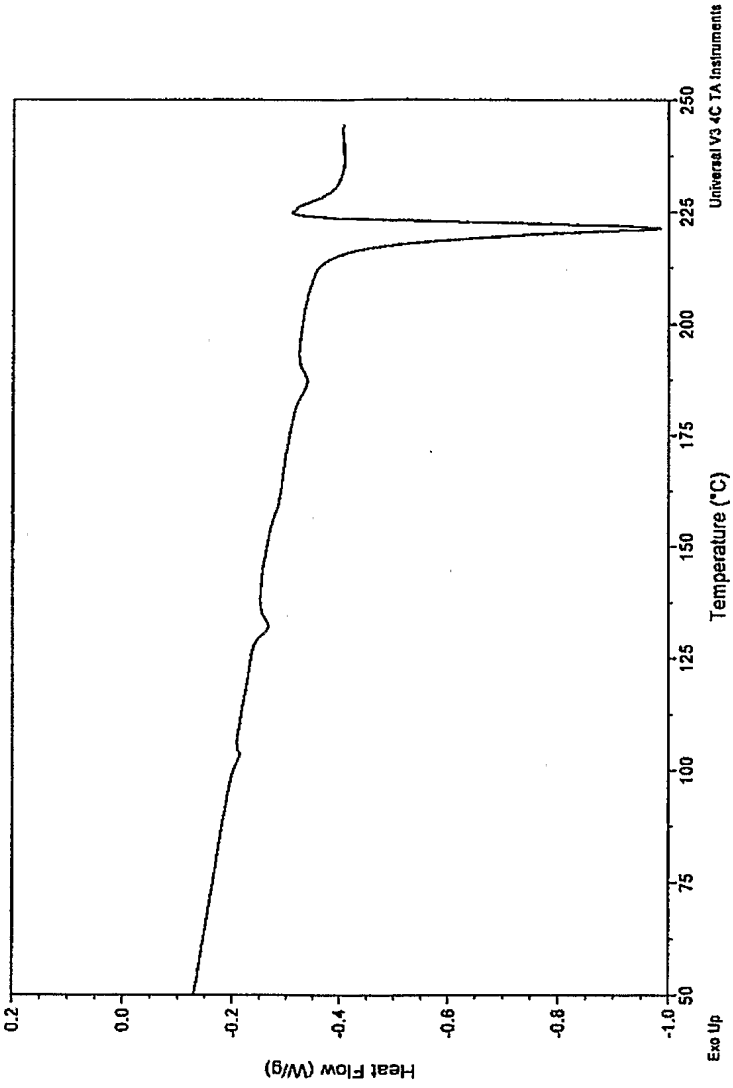



Fig. 6

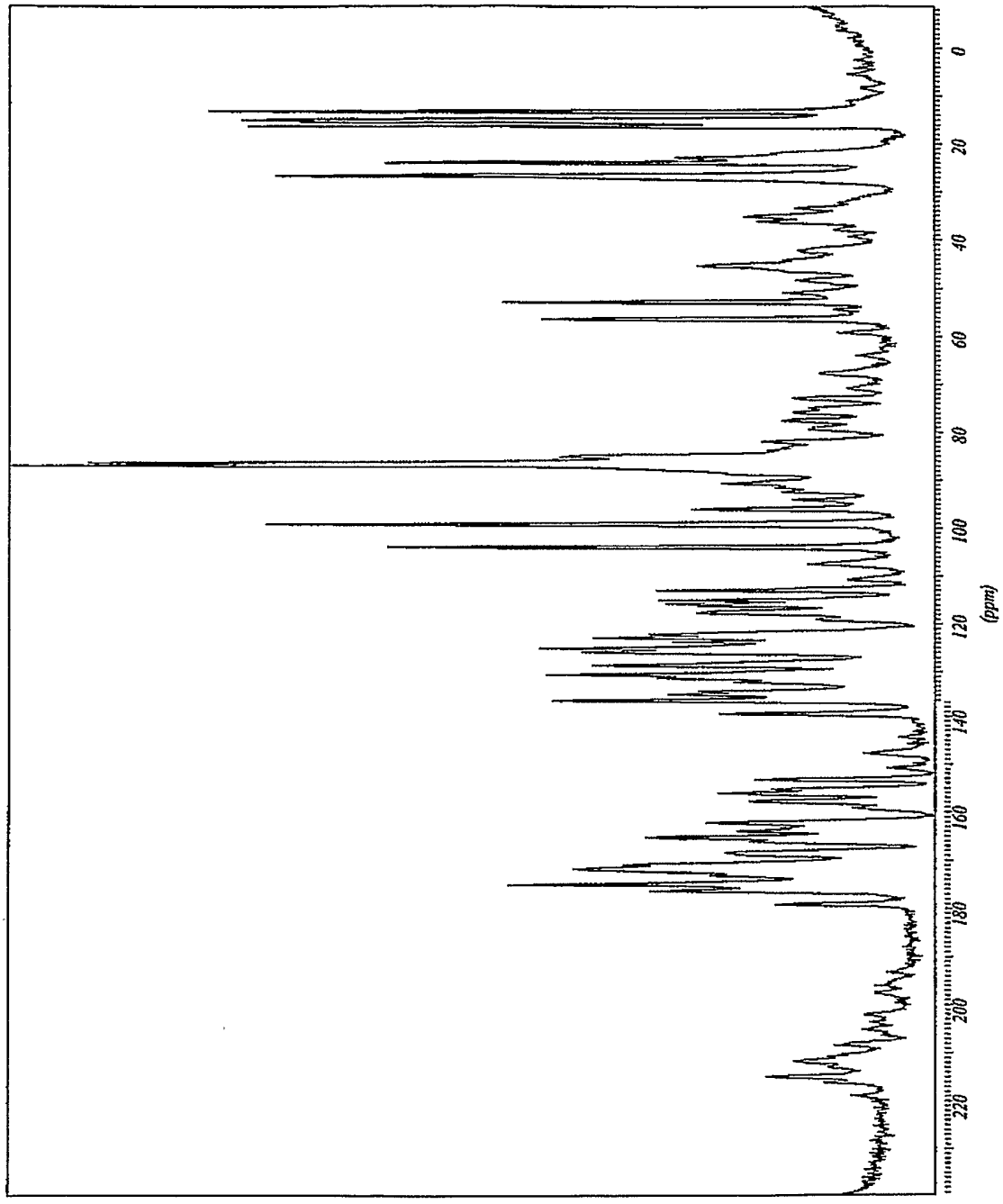



Fig. 7

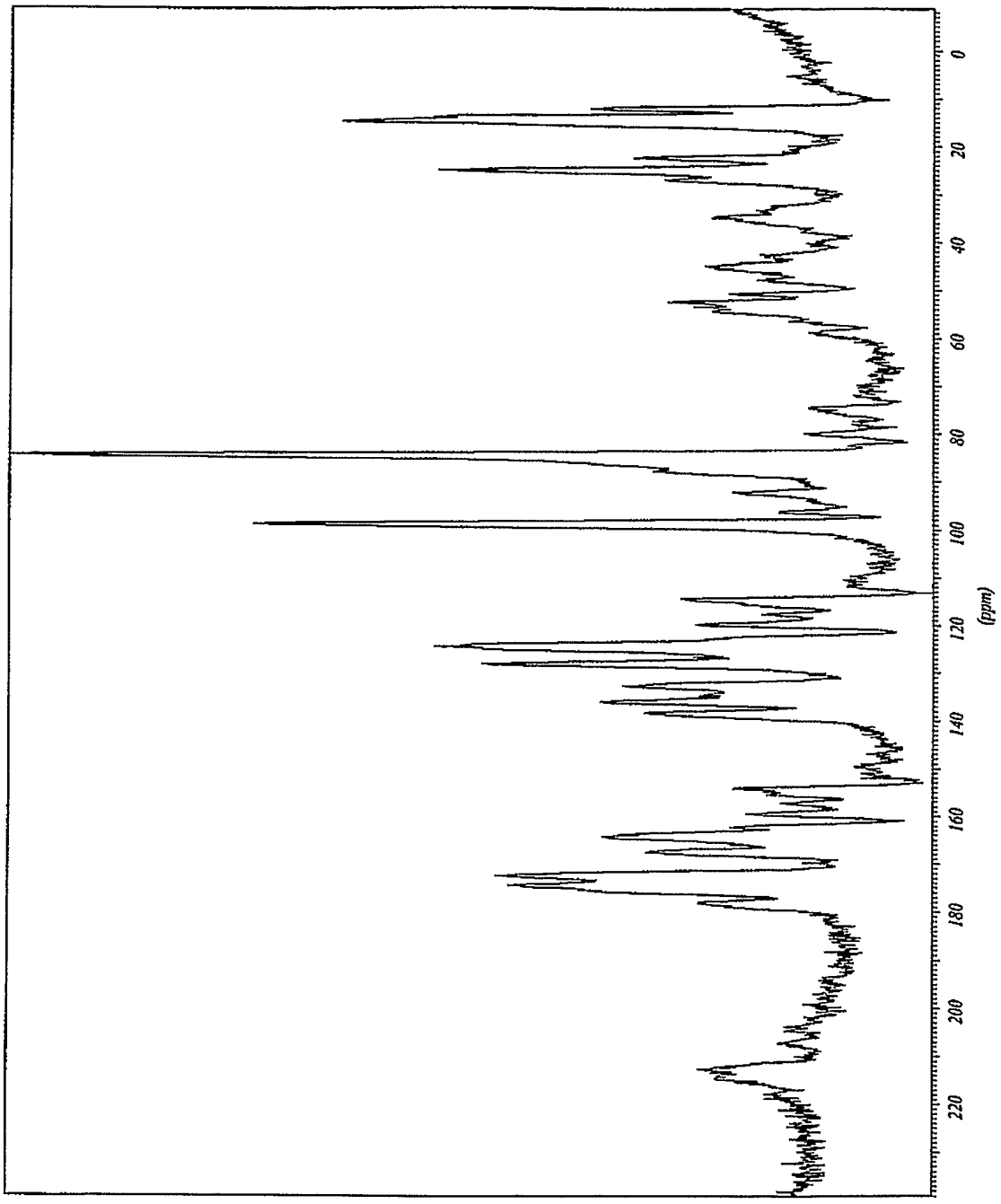



Fig. 8

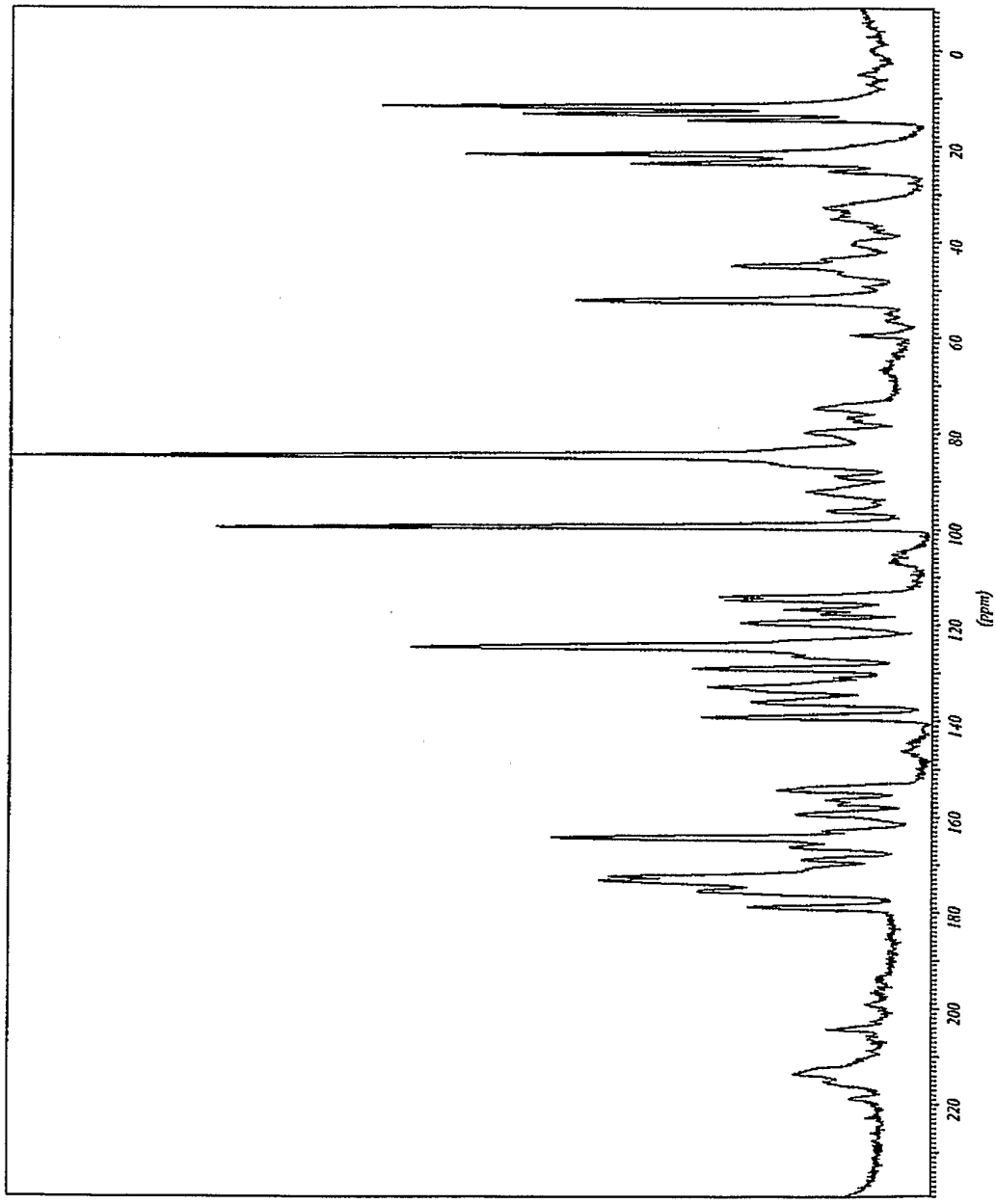



Fig. 9

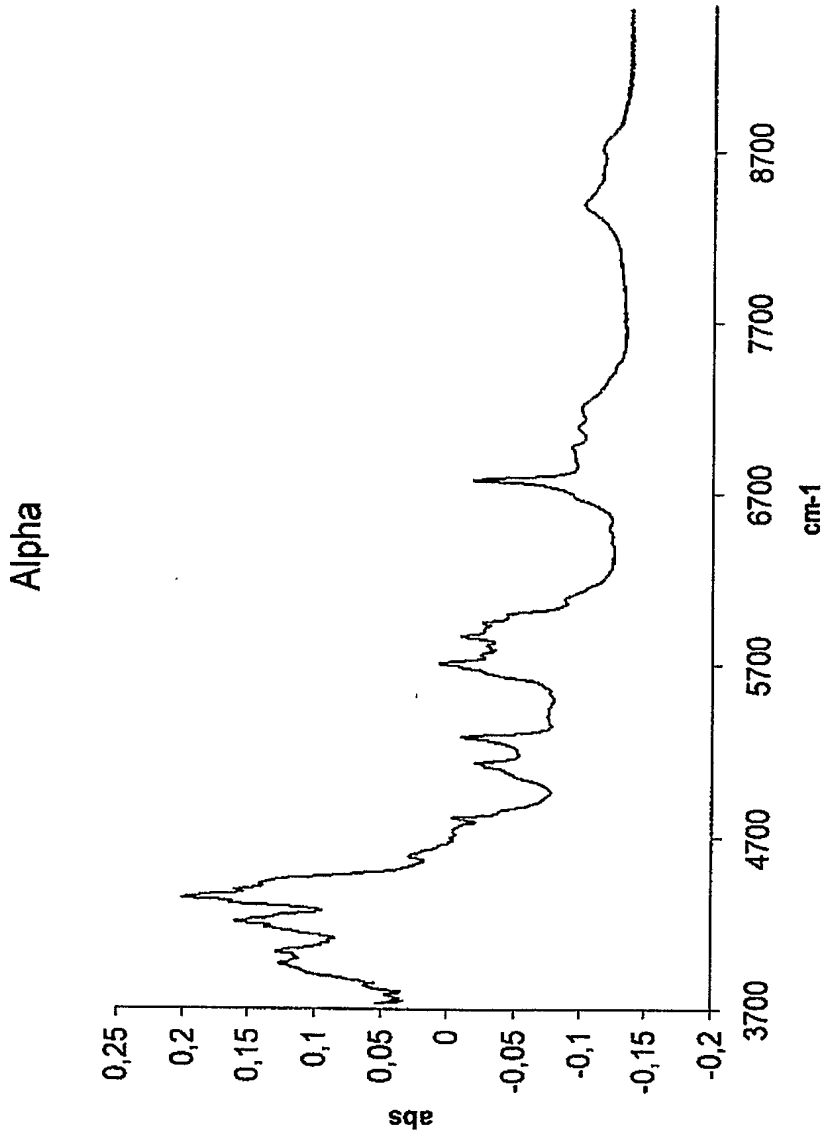



Fig. 10

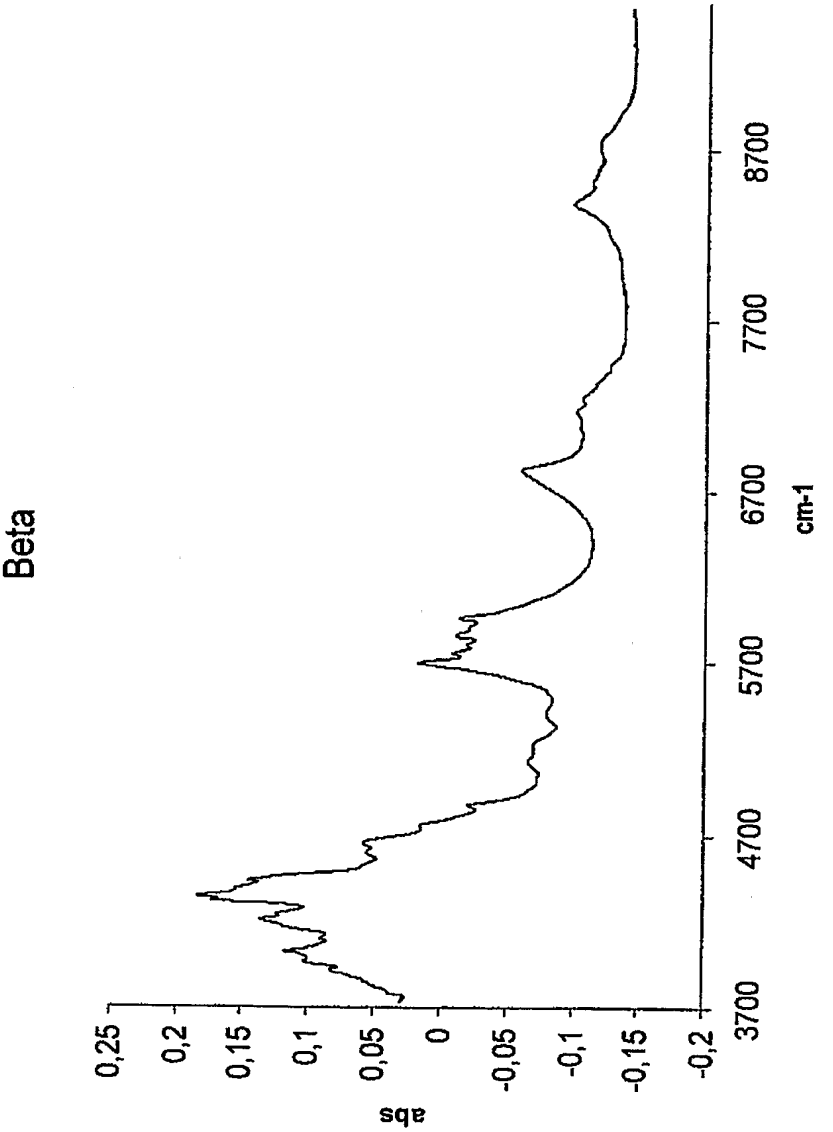



Fig. 11

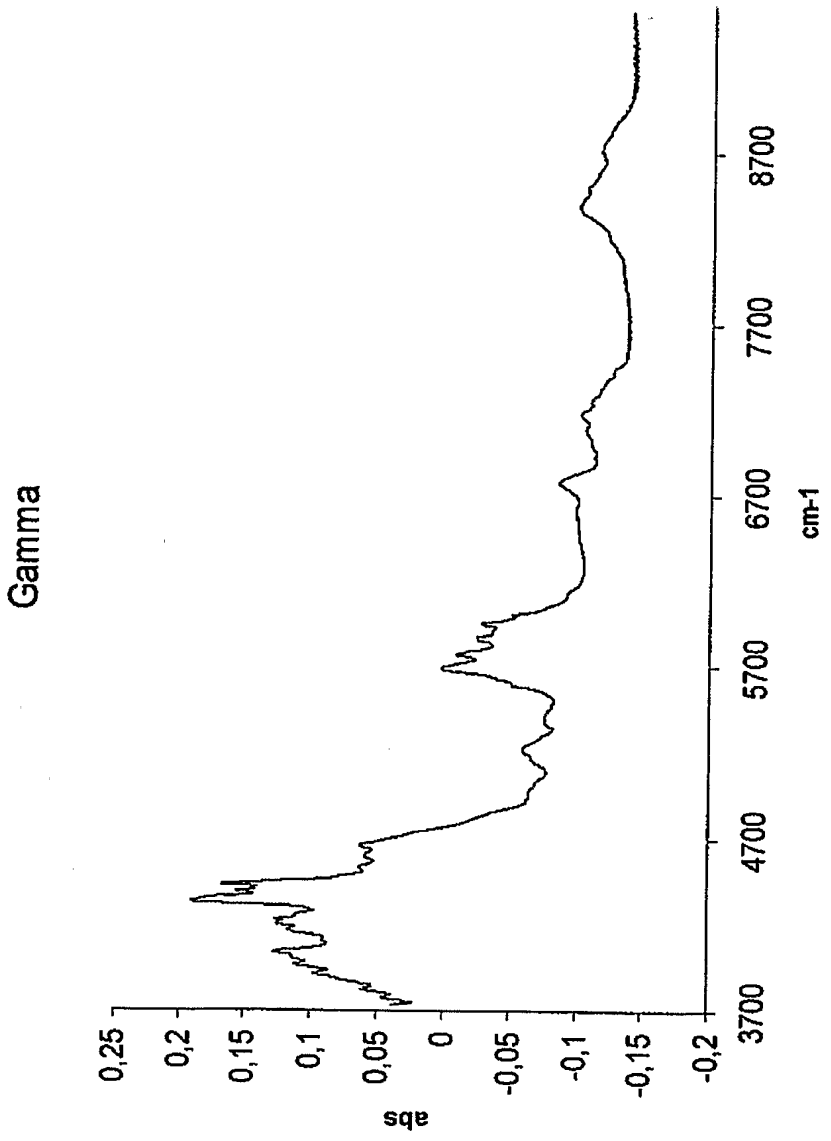



Fig. 12